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CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER

NIEBAUER, RONALD T

ART UNIT	PAPER NUMBER
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1654

NOTIFICATION DATE	DELIVERY MODE
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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No. 10/516,079	Applicant(s) ALVAREZ ET AL.	
	Examiner RONALD T. NIEBAUER	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,9-12 and 18-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,9-12,18-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants amendments and arguments filed 6/9/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 7-8,13-17 are cancelled. Claims 6,11 have been amended. Claims 1-6,9-12,18-21 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

This rejection is maintained from the previous office action.

Claims 1-6,9-12,18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention.” Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008,

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1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (“[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.”). Thus, an applicant complies with the written description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.” *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

“A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) (“In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...”) *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts

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determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include “level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.” MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to methods or compositions of chlorotoxin or chlorotoxin derivatives.

(1) Level of skill and knowledge in the art:

The level of skill in the art is high.

(2) Partial structure:

The claims (claims 1,9,14 and dependent claims) recite that the chlorotoxin derivative can comprise particular sequences, portions thereof, and combinations thereof. There are many peptides within the genus. For example SEQ ID NO:13 (TTX1X2X3MX4X5K) which is 9 amino acids in length can have any amino acid at position X2 and X4 and numerous amino acids at X1,X3,X5. In considering the possible variability, there are over 4800 different 9 amino acid

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peptides possible. Further, there are many peptide portions and combinations of peptides. Hence, there is substantial variability in the genus.

The sequence listing includes 95 sequences (some of which may not be applicable to the current argument). Since the genus includes well over 4800 different sequences, the 95 sequences do not even represent two percent of the peptides within the genus.

Since there are a substantial variety of polypeptides possible within the genus, the examples do not constitute a representative number of species and do not sufficiently describe the genus claimed (see Gostelli above).

(3) Physical and/or chemical properties and (4) Functional characteristics:

The claims recite that the chlorotoxin derivatives, portions thereof and combinations thereof are useful for treating cancer. However, limited direction is provided as to what portions are necessary to be useful in treating cancer. As claimed, any portion or combination would meet the claim limitations. Limited direction is provided as to what portions or combinations are useful in treating cancer. The specification (page 10 lines 25-32) recites the phrase core binding sequences, however no common core is taught for all of the derivatives. One of skill in the art would not recognize which portions and combinations would be useful for treating cancer.

(5) Method of making the claimed invention:

Synthesis of peptides is described in example 11.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 1,9,14 and dependent claims is/are broad and generic, with respect to all possible derivatives

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encompassed by the claims. The possible structural variations are limitless to any derivative. Although the claims may recite some functional characteristics, the claims lack written description because there is limited disclosure of a correlation between function and structure of the polypeptides beyond those polypeptides specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of polypeptides identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of polypeptides embraced by the claims.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does “little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.”) Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention

Response to Arguments 112 Written Description

Applicants argue that the relevant analysis is not related to the possible number of peptides encompassed by the claims. Applicants argue that the Written Description Training Manual (Example 5) includes an example that recites ‘comprising’ a protein that includes a particular amino acid sequence. Applicants argue that relevant identifying characteristics are

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described in the instant specification and that specific experiments and examples in the specification relate structure to function.

Applicant's arguments filed 6/9/08 have been fully considered but they are not persuasive.

Although applicants argue that the relevant analysis is not related to the possible number of peptides encompassed by the claims, section 2163 II A 2 a (ii) of the MPEP states that when there is substantial variation within the genus that one must describe a sufficient variety of species to reflect the variation within the genus and further states ' If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description'. As such, consideration of a representative number of species is relevant.

In the instant case the claims are drawn to specific sequences and portions thereof, and combinations thereof. For example SEQ ID NO:1 is MCMPCFTTDHQMARCDDCCGGKGRGKCYGPQCLCR. As such CR (a portion) is a member of the genus. CFCL is a member of the genus (a combination of portions). Further, PCFT, PCR,PC,CRK, etc. are members of the genus of portions and combinations thereof. Hence there is substantial variability in the genus. Of the genus of portions thereof and combinations thereof, there is no required core structure. For example M (a portion) and MQ (a combination of portions) are members of the genus. A single amino acid is not recognized as a core structure.

Further, as noted by applicant, the specification (page 10 lines 25-32) teaches that the chlorotoxin derivatives retain the same activity as chlorotoxin. Therefore, guidance is necessary

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to determine what portions and combinations are correlated with the required chlorotoxin activity.

Although applicants make arguments relating to Written Description Training Manual Example 5, such example is not drawn to portions thereof, and combinations thereof. Although applicants argue that relevant identifying characteristics are described in the instant specification and examples, such examples are not commensurate with the scope of the instantly claimed genus. In particular, example 11 is drawn to 10mer peptides while the instant claims are drawn to any length of portions (can be 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9, etc amino acids in length). One of skill in the art would not recognize that data relating to 10mer peptides to be applicable to correlations to any and all portions and combinations thereof. Example 13 relates to peptides of 6 amino acids in length or greater. Example 14 relates to sequences in which single residues are substituted with alanine. Specific examples of combinations of portions are not found in the instant specification. In relation to the instant genus, the examples provided do not describe which amino acids (commensurate in scope with the instant genus) can be deleted to arrive at portions thereof with the required activity. Likewise, the examples do not describe which amino acids portions (commensurate in scope with the instant genus) can be combined to arrive at combinations thereof with the required activity. One of skill in the art would not recognize that the disclosure of specific sequences as representative of combinations and portions thereof.

Further, the knowledge in the art is that conservation of structure is not equal to conservation of function. When non-exchange group members of amino acids are substituted (such as proline for tryptophan) the expectation is that the substitution would not likely conserve the structure or function. When amino acids are deleted or when portions or combinations of

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amino acids are combined one would not necessarily have an expectation that such portions and combinations would have the same function as the full length peptide nor would one expect to be able to correlate from a limited data set which portions or combinations would have the required function. The specification only provides limited guidance on portions of peptides and without further testing one of skill in the art would not be able to identify which portions and combinations have the required function. In other words combinations (such as CFCL) and portions (such as CR) would be expected to vary unpredictably from the function and properties of MCMPCFTTDHQMARCDDCCGGKGRGKCYGPQCLCR. In an unpredictable art, written description is not achieved by disclosure of a limited number of species. The specification does not describe sufficiently detailed, relevant characteristics to show that the applicant was in possession of the instantly claimed genus.

Recently in Ex Parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), Board of Patent Appeals and Interferences, found lack of written description in a claim drawn to a genus of polynucleotides encoding polypeptides “at least 80% identical to amino acids 22-221 of SEQ ID NO:2” The Board stated:

“Claim 73 is to a genus of polynucleotides encoding polypeptides “at least 80% identical to amino acids 22-221 of SEQ ID NO:2” which bind to CD48. Sufficient description to show possession of such a genus “may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus.” *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

In this case, Appellants have sequenced two nucleic acids falling within the scope of claim 73 and three fusion proteins whose nucleotide sequences would fall within the scope of claim 73. None of these sequences varies amino acids 22-221 of NAIL, and thus these sequences are not representative of the genus.

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Appellants also have described how to make and test other sequences within claim 73 sufficiently to satisfy the enablement requirement. **However, they have not described what domains of those sequences are correlated with the required binding to CD48, and thus have not described which of NAIL's amino acids can be varied and still maintain binding. Thus, under *Lilly* and its progeny, their Specification would not have shown possession of a sufficient number of sequences falling within their potentially large genus to establish possession of their claimed genus. Cf. *Enzo*, 323 F.3d at 964, 63 USPQ2d at 1612 (“if the functional characteristic of ... binding to [CD48] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed,” the written description requirement may be met).**

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (“definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is”). See *Kubin* at 1417.

Here, similar to *Kubin*, the specification fails to adequately describe what domains (and portions and combinations thereof) of the sequences are correlated with the required activity, and thus have not described which of the amino acids can be deleted or varied and still maintain the required activity. Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

For these reasons and the reasons set forth previously Claims 1-6,9-12,18-21 remain rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

This rejection is maintained from the previous office action.

Claims 1,4-6,9-12,18-20 remain rejected under 35 U.S.C. 102(e) as being anticipated by Samoylova et al. (US 2003/0216322 as cited previously) as evidenced by Merck Manual (on-line version www.merck.com/mmhe ‘methotrexate’ entry as cited previously).

Samoylova teach peptides for recognition and targeting of glial cell tumors (title). Samoylova teach compositions comprising a peptide and a chemotherapeutic agent (claim 4, section 0068) (compare claim 9 of the current invention). Samoylova teach peptides such as ELRGDSLP (claim 6), which comprises a portion (RG, amino acids 25 and 26 of chlorotoxin SEQ ID NO:1 of the current invention) of chlorotoxin thus meeting the structural limitations of a portion of a chlorotoxin derivative as recited in claims 1,9 and dependent claims. Samoylova teach chemotherapeutic agents such as methotrexate (section 0066) (compare claim 11,6 of the current invention). The Merck Manual teaches (page 2) that methotrexate is an anti-metabolite (a universal fact so priority date not relevant - see MPEP 2124) (compare claim 10,5 of the current invention).

Samoylova teach a need for therapies for brain tumor patients (section 0008) and specifically teach patient populations with glioblastomas (section 0004). Samoylova teach the administration of a peptide conjugated to a chemotherapeutic agent (methotrexate) in example 3 specifically section 0132 (compare claim 4,18,20 of the current invention) and further

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experiments in human patients (example 4 section 0135). In addition to simultaneous administration via a conjugate, Samoylova teach compositions in which the peptide and chemotherapeutic agent are not conjugated to one another (section 0068). Samoylova teach compositions with a pharmaceutically acceptable carrier (section 0069) (compare claim 19 of the current invention).

Regarding claim language, section 2111.04 of the MPEP states:

Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

..... a “whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.”

In the instant case, the recitation ‘for treating cancer’ (claim 9) does not limit the claim to a particular structure. The recitation ‘wherein the cancer is ...’ (claim 12) does not limit the claim to a particular structure.

Response to Arguments 102

Applicants argue that the claims are drawn to ‘chlorotoxin derivatives’ which has been described in the specification as meaning derivatives which retain the same activity as chlorotoxin. Applicants argue that there is no evidence that the peptides of Samoylova retain the same activity as chlorotoxin and thus cannot anticipate the claimed invention.

Applicant's arguments filed 6/9/08 have been fully considered but they are not persuasive.

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Although applicants argue that the peptides of Samoylova do not have the required function, Samoylova teach peptides such as ELRGDSLP (claim 6), which comprises a portion (RG, amino acids 25 and 26 of chlorotoxin SEQ ID NO:1 of the current invention) of chlorotoxin thus meeting the structural limitations of a portion of a chlorotoxin derivative as recited in claims 1,9 and dependent claims. Since the peptides of Samoylova have the required structure they necessarily have the required function (see MPEP section 2112.01). In particular, section 2112.01 of the MPEP states 'A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.' Since Samoylova teach peptides such as ELRGDSLP (claim 6), which comprises a portion (RG, amino acids 25 and 26 of chlorotoxin SEQ ID NO:1 of the current invention) of chlorotoxin the claimed properties are necessarily present.

Further, the specification states that activity is activity such as binding specifically to a cancer cell when compared to a normal cell (page 10 lines 25-32). Samoylova teach that the peptides such as ELRGDSLP exhibit preferential binding to glioma cells (claim 1,6) and state that the (Figure 5 section 0023) peptide ELRGDSLP is selective for glioma cells compared to control cells. As such, contrary to applicants assertion, there is evidence that the peptides of Samoylova retain the same activity as chlorotoxin, such as binding specifically to a cancer cell when compared to a normal cell.

For these reasons and the reasons set forth previously Claims 1,4-6,9-12,18-20 remain rejected.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

This rejection is maintained from the previous office action.

Claims 1-6,9-12,18-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Samoylova et al. (US 2003/0216322 as cited previously) and Stupp et al. (The Lancet v2 Sept 2001 552-560 as cited previously).

As discussed above, Samoylova teach peptides for recognition and targeting of glial cell tumors (title). Samoylova teach compositions comprising a peptide and a chemotherapeutic agent (claim 4, section 0068) (compare claim 9 of the current invention). Samoylova teach a need for therapies for brain tumor patients (section 0008) and specifically teach patient populations with

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glioblastomas (section 0004). Samoylova teach the administration of a peptide conjugated to a chemotherapeutic agent (methotrexate) in example 3 specifically section 0132 (compare claim 4,18,20 of the current invention) and further experiments in human patients (example 4 section 0135). In addition to simultaneous administration via a conjugate, Samoylova teach compositions in which the peptide and chemotherapeutic agent are not conjugated to one another (section 0068). Samoylova teach compositions with a pharmaceutically acceptable carrier (section 0069) (compare claim 19 of the current invention).

Samoylova et al. does not expressly recite an embodiment with chlorotoxin as the peptide (instead Samoylova teach phage derived peptides). Samoylova does not expressly teach the chemotherapeutic agent temozolomide.

Samoylova does teach chlorotoxin (section 0010) (equivalent to SEQ ID NO:1 of the current invention, the elected species of chlorotoxin) as a peptide that specifically binds to glioma cells. Since Samoylova also teach that the peptides of the invention are cell-binding peptides (section 0034) one would be motivated to substitute the chlorotoxin peptide for the phage derived peptides particularly since Samoylova specifically teach glioma as a target and also since chlorotoxin is taught to have high-affinity specific binding to glioma cells (section 0010).

Stupp teach the administration of the alkylating agent/chemotherapeutic agent temozolomide (abstract) (compare claims 5,6,10,11 of the current invention). Stupp specifically teach temozolomide for brain tumours and glioma (abstract). Stupp teach temozolomide with other active agents against brain tumours (abstract and page 557-558). Stupp specifically teach that temozolomide can be used sequentially with other agents (page 557 1st column last

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paragraph) and also in a variety of combination dosing schedules (page 557-558) (compare claims 2-3 of the current invention), and in combination with more than one agent (page 558 first column last paragraph) (compare claim 21 of the current invention).

One would have been motivated to combine the chemotherapeutic agent temozolomide as taught by Stupp into the method/compositions of Samoylova since both references deal with therapeutics specifically of brain tumors. Both references motivate the use of combination therapies. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Further, it is noted that it is obvious to combine known elements to be used for the same purpose and that the motivation to combine them flows logically from their being taught in the prior art (MPEP 2144.06). In the instant case, both chlorotoxin and temozolomide were each individually taught in methods and compositions for treating brain tumors.

It has been recently held that “Neither §103's enactment nor *Graham's* analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art.” KSR v. Teleflex, 550 U.S. ___, 82 USPQ2d 1385, 1389 (2007). The KSR court stated that “a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” KSR at 1389. The Supreme Court stated that there are “[t]here cases decided after *Graham* [that] illustrate this doctrine.” KSR at 1395. “In United States v. Adams, 383 U.S. 39, 40, 148 USPQ 479 (1966) . . . [t]he Court recognized that when a patent claims a structure already known in the

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prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.” KSR at 1395. Thus, the mere substitution of one known element for another to obtain a predictable result is obvious.

Furthermore, The KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR*

When there is motivation

"to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

In the instant case, Samoylova teach phage derived peptides. Since the peptides are taught as cell-binding peptides (section 0034) and chlorotoxin is a specific cell binding peptide, one would have substituted the known elements (chlorotoxin for the phage derived peptides) and would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant case, all the claimed elements were taught in the prior art (Samoylova – chlorotoxin; Stupp – temozolomide) and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response to Arguments 103

Applicants argue that although Samoylova teach chlorotoxin peptide as having binding activity to glioma cells there is no direction toward chlorotoxin peptides for use in treating

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gliomas. Applicants argue that there is no explanation why one would be motivated to substitute a chlorotoxin peptide for one of the other peptides that bind glioma cells.

Applicant's arguments filed 6/9/08 have been fully considered but they are not persuasive.

Samoylova teach peptides for recognition and targeting of glial cell tumors (title) and compositions for use in therapy of cancer cells (abstract). Samoylova teach a need for therapies for brain tumor patients (section 0008) and specifically teach patient populations with glioblastomas (section 0004). Samoylova teach the administration of a peptide in example 3 specifically section 0132 (compare claim 4,18,20 of the current invention) and further experiments in human patients (example 4 section 0135). As such, the recognized problem is effective therapy of gliomas, specifically using peptides that bind to gliomas with high specificity (section 0032).

Samoylova teach peptides that bind to glioma cells that were identified using a phage display library (section 0037-0038, claim 10). Samoylova teach that the peptides were isolated for the ability to bind glioma cells (section 0037).

Samoylova teach (section 0010) that the peptide chlorotoxin shows high-affinity, specific binding to glioma cells. Samoylova even goes so far as to provide a further suggestion that the chlorotoxin peptide may find use in therapeutic applications (section 0010). As such, there is an express suggestion within the reference to modify the reference contrary to applicants assertion that there is no direction toward the use of chlorotoxin peptides. Further, a disclosure of alternate peptides with specific functions does not discredit one peptide over the other.

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Taken together, Samoylova teach peptides such as the peptide of claim 10 that binds to gliomas with high specificity. Further, Samoylova teach that the peptide chlorotoxin shows high-affinity, specific binding to glioma cells (section 0010). Therefore the peptide of claim 10 and the chlorotoxin peptide were known in the art as well as their ability to bind to gliomas with high specificity.

Since Samoylova teach that the invention is drawn to peptides that have been shown to bind glioma cells with high specificity (section 0032) one would be motivated to use peptides that bind glioma cells with high specificity such as the chlorotoxin peptide or the peptide of claim 10.

Therefore, the claims would have been obvious because the substitution of one known element (chlorotoxin) for another (the peptide of claim 10 of Samoylova) would have yielded predictable results to one of ordinary skill in the art at the time of the invention. It is noted that Samoylova teach that chlorotoxin and the peptide of claim 10 bind to gliomas with high specificity thus one would have a reasonable expectation of success.

For these reasons and the reasons set forth previously Claims 1-6,9-12,18-21 remain rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

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Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

These rejections are maintained from the previous office action.

Claims 9-12 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,13 of copending Application No. 10/522,810 ('810) in view of Stupp et al. (The Lancet v2 Sept 2001 552-560).

'810 teach a subunit of chlorotoxin (i.e. a portion of chlorotoxin - compare claim 9 of the current invention) in a composition conjugated to a cytotoxic agent for binding to cancer cells (claim 13).

'810 does not teach the specific cytotoxic agent of the current invention.

Stupp specifically teach temozolomide compositions for brain tumours and glioma (abstract). Stupp teach temozolomide with other active agents against brain tumours (abstract and page 557-558). Stupp teach that temozolomide is a cytotoxic agent (page 553 2nd full paragraph line 13). As discussed above it would have been obvious to substitute the agent of Stupp into other compositions such as that of '810 that target cancer cells.

This is a provisional obviousness-type double patenting rejection.

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Claim 1 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,23 of copending Application No. 11/731,661 ('661).

'661 teach a method of administering a chlorotoxin conjugate (claim 1) and a chemotherapeutic agent (claim 23) to a patient with tumors which reads on claim 1 of the current invention.

This is a provisional obviousness-type double patenting rejection.

Claims 1-6,9-12,18-21 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,23 of copending Application No. 11/731,661 ('661) in view of Samoylova et al. (US 2003/0216322) and Stupp et al. (The Lancet v2 Sept 2001 552-560).

'661 teach a method of administering a chlorotoxin conjugate (claim 1) and a chemotherapeutic agent (claim 23).

As discussed above, Samoylova and Stupp teach the remaining claim limitations. In the instant case, all the claimed elements were taught in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

This is a provisional obviousness-type double patenting rejection.

Claims 1,4,9 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4,21 of copending Application No. 11/547,875 ('875) in view of Stupp et al. (The Lancet v2 Sept 2001 552-560).

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‘875 teach administration of a composition comprising chlorotoxin (claim 4) and a cytotoxic agent (claim 21) to patients with cancer.

‘875 does not teach the specific cytotoxic agent of the current invention.

Stupp specifically teach temozolomide compositions for brain tumours and glioma (abstract). Stupp teach temozolomide with other active agents against brain tumours (abstract and page 557-558). Stupp teach that temozolomide is a cytotoxic agent (page 553 2nd full paragraph line 13). As discussed above it would have been obvious to substitute the agent of Stupp into other compositions such as that of ‘875.

This is a provisional obviousness-type double patenting rejection.

Claims 1-6,9-12,18-21 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4,21 of copending Application No. 11/547,875 (‘875) in view of Stupp et al. (The Lancet v2 Sept 2001 552-560) and Samoylova et al. (US 2003/0216322).

‘875 teach administration of a composition comprising chlorotoxin (claim 4) and a cytotoxic agent (claim 21) to patients with cancer.

As discussed above, Samoylova and Stupp teach the remaining claim limitations. In the instant case, all the claimed elements were taught in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

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The claims as specified above are directed to an invention not patentably distinct from the claims specified above of commonly assigned 10/522,810; 11/731,661; 11/547,875.

Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300).

Commonly assigned 10/522,810; 11/731,661; 11/547,875, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments Double Patenting

Applicants argue that the rejection will be addressed upon indication of an allowance of the presently pending case.

Applicant's arguments filed 6/9/08 have been fully considered but they are not persuasive.

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Applicant has not overcome the rejections and there is no indication of an allowance, thus the rejections are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654